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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,480	10/23/2003	Silviu Itescu	0575/66602-B/JPW/BJA	2572

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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
05/15/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/693,480	ITESCU, SILVIU	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2012*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *35,37,43,46,47,49-51 and 57* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *35,37,43,46,47,49-51 and 57* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *01 February 2008 and 23 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/15/2012*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 15 March 2012 has been entered in full. Claim 35 is amended, Claims 1-34, 36, 38-42, 44-45, 48, and 52-56 are cancelled.

Claims 35, 37, 43, 46, 47, 49-51 and 57 are under consideration in the instant application.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 15 March 2012 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. It is noted that Norrby et al. (citation #6) and Yanagisawa et al. (citation #8) were crossed off by the Examiner because the references were illegible. The words in the references were very dark and blurred together.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1. Claims 35, 37, 43, 46-47, 49, 50, 51 and 57 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 7,662,392. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a method of treating a disorder of the heart comprising administering stromal-derived factor-1. The basis for this rejection is set forth at pages 3-6 of the previous Office Action of 15 September 2011, pages 2-5 of the Office Action of 18 January 2011, pages 2-3 of the Office Action of 18 September 2009, pages 2-3 of the Office Action of 03 February 2009, page 4 of the Office Action of 09 May 2008 and pages 6-7 of the Office Action of 08 August 2007.

At the top of page 5, Applicant indicates the consideration of filing a terminal disclaimer over U.S. Patent should the claims of the subject application otherwise be deemed allowable.

The rejection is maintained and held in abeyance until all other issues are resolved. However, Applicant is encouraged to submit a terminal disclaimer at Applicant's earliest convenience.

2. Claims 35, 37, 43, 46-47, 49-51, and 57 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 69, 70, 72-75, 77-78 of copending Application No. 12/657,264. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a method of administering stromal-derived factor-1. The basis for this rejection is set forth at pages 6-7 of the previous Office Action of 15 September 2011.

At the middle of page 5 of the Response of 15 March 2012, Applicant states that the provisional rejection over claims 69, 70, 72-75, 77, and 78 of copending U.S. Serial No. 12/657,264 should be withdrawn if the claims of the subject application are otherwise allowable.

The provisional rejection is maintained and held in abeyance until all other issues are resolved.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 35, 37, 43, 46, 47, 49-51, and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isner et al. (WO 99/45775), Watanabe et al. (Basic Res Cardiol 93: 30-37, 1998) and Rempel et al. (Clin Can Res 6: 102-111, 2000). The basis for this rejection is set forth at pages 7-10 of the previous Office Action of 15 September 2011.

Applicant's arguments (15 March 2012), as they pertain to the previous rejection of record have been fully considered but are not deemed to be persuasive for the following reasons.

(i) At the top of page 7, Applicant argues that the cited prior art teach systemic administration of the particular vascularization agent claimed, i.e. SDF-1. Applicant asserts that the cited references neither teach a method involving "intramyocardially or intracoronarily administering to the subject an amount of an agent comprising a human stromal derived factor-1", as recited in the pending claims, nor provide a basis to reasonably expect such a method to be successful. At the middle of page 7 of the Response, Applicant submits that Isner et al. disclose that systemic (i.e., subcutaneous) administration of vascularization agents, such as GM-CSF, is required to mobilize EPCs which then migrate to a site of ischemic to enhance neovascularization. Applicant argues that Isner et al. do not differentiate between vascularization agents or teach or suggest that SDF-1 could or should be administered differently than GM-CSF. Applicant asserts that Isner et al. does not provide any reason for a person of skill in the art to seek out complex intramyocardial or intracoronary administration of any of its vascularization agents. Applicant adds that Watanabe et al. only disclose a specific method for administering a particular vascularization agent, FGF-2 and that the relation of FGF-2 to the claimed agent, SDF-1, is unclear except that both are vascularization agents.

Applicant's arguments have been fully considered but are not found to be persuasive. As discussed in the previous Office Action, Isner et al. teach a methods for inducing angiogenesis in ischemic tissue of patient in need of such treatment by administration of a vascularization modulating agent (page 14, lines 18-21). Isner et al. teach that the vascularization modulating agent may be SDF-1 (page 21, lines 13-18). Isner et al. continue to disclose that method of the

invention may be used to prevent or treat ischemic cardiomyopathy, cerebrovascular ischemia, and myocardial ischemia (page 15, lines 1-5). It is well known in the art that there is a loss or apoptosis of cardiomyocytes in acute myocardial ischemic injury as evidenced by Buja et al. (Cardiovasc Pathol 17(6): 349-374, 2008;; see pages 358-362; Figure 3). Isner et al. teach that ischemia may adversely impact heart or brain tissue (page 15, lines 8-10). Isner et al. also state that administration of the agent may be parenterally, including subcutaneous, intravenous, intraarterial, intramuscular, and intraperitoneal (page 18, lines 16-19).

Although Isner et al. does not specifically disclose intramyocardial or intracoronary administration of SDF-1, Watanabe et al. teach that administration of growth factors is emerging as a new therapeutic approach for the enhancement of collateral vessel formation in the ischemic heart (abstract). Watanabe et al. disclose that the growth factor, FGF-2 (or bFGF), is injected alone or with heparin or heparan sulfate into normal myocardium and the border zone of ischemic myocardium in a porcine myocardial infarct model (page 31, column 1, middle of second paragraph; abstract; Figure 1). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of administering of SDF-1 to a subject suffering from ischemic cardiomyopathy, cerebrovascular ischemia, and myocardial ischemia as taught by Isner et al. by intramyocardially administering human SDF-1α or SDF-1β as taught by Rempel et al. and Watanabe et al. The person of ordinary skill in the art would have been motivated to make that modification in order to localize angiogenesis or induction of collateral vessels to the ischemic heart of the patient. The person of ordinary skill in the art reasonably would have expected success because (i) similar angiogenic growth factors were

already being intramyocardially administered to the heart at the time the invention was made and (ii) SDF-1α and SDF-1β are isoforms encoded from the SDF-1 gene.

(ii) At the top of page 7 of the Response, Applicant contends that the conflicting prior art as a whole shows confusion in the field about whether intramyocardial administration of a vascularization agent is effective. At the middle of page 8 of the Response, Applicant contends that there is no evidence of record showing that the teaching of Watanabe et al., e.g. intramyocardial administration of FGF-2, could be generalized to all vascularization agents. Applicant argues that a person of ordinary skill in the art could not reasonably determine whether other vascularization agents, such as those disclosed in Isner et al., would have similar effects as FGF-2 when administered intramyocardially. Applicant cites Hung et al. (US 2003/0171294) and states that intracoronary administration of FGF-2 is ineffective. Applicant argues that Hung et al. discloses that administration of FGF polypeptide to the ameroid model provided no benefit over placebo. Applicant points out that Hung et al. show intramyocardial or intracoronary administration of FGF polypeptide is not effective for treating a disorder of heart tissue involving loss or apoptosis of cardiomyocytes, Watanabe et al. show that intramyocardial administration of FGF-2 could increase the number of arterioles in infarct border area. Applicant concludes that a person of ordinary skill would understand that these references to at best evidence confusion in the art about the effects of intramyocardial administration of FGF-2. At the bottom of page 9 of the Response, Applicant submits that the teaching of Hung et al. conflicts with the teaching of Watanabe et al. Applicant argues that weighing all the teachings of the prior art, a person of ordinary skill in the art is likely to understand that a disorder of a heart tissue involving loss or

apoptosis of cardiomyocytes may not be treatable by intramyocardial administration of a vascularization agent, FGF-2, which is consistent with the teaching of Hung et al. while not inconsistent with the teaching of Watanabe et al.

Applicant's arguments have been fully considered but are not found to be persuasive. Watanabe et al. teach that "a number of studies have shown that delivery of oxygenous growth factors enhance angiogenesis in animal models of myocardial ischemia" (page 30, bottom of column 2). In support of intracoronary or intramyocardial administration of growth factors, Watanabe et al. disclose that large doses of FGF-2 or VEGF are required for improved collateral blood flow when they are systemically administered due to their short half-life in circulation (page 35, column 2, 3rd full paragraph). Watanabe et al. indicate that systemic delivery of such large doses of growth factors might result in uncontrolled growth of latent tumors or progression of diabetic retinopathy (page 35, column 2, 3rd full paragraph). Watanabe et al. state that intra-arterial administration of FGF-2 and VEGF are associated with a decrease in blood pressure and moderate anemia indicating systemic administration is not a favorable treatment for patients suffering heart failure (page 35, column 2, 3rd full paragraph). Hence, the state of the art at the time of filing the instant application recognized that intracoronary or intramyocardial administration of growth factors may be the most effective means to enhance angiogenesis or induction of collateral vessels to an ischemic heart (see Watanabe et al., page 36, column 2; page 31, column 1, 2nd full paragraph).

Although Applicant argues that conflicting prior art as a whole shows confusion in the field about whether intramyocardial administration of a vascularization agent is effective (citing Hung et al., US 2003/0171294), Watanabe et al. clearly teach that when FGF-2 (or bFGF), is

injected alone or with heparin or heparan sulfate into normal myocardium and the border zone of ischemic myocardium in a porcine myocardial infarct model, the delivery of FGF-2 increases the density of arterioles in normal myocardium and the border zone area (page 31, column 1, middle of second paragraph; abstract; Figure 1; page 34; page 35, top of column 1). Watanabe et al. also teaches that recent studies concerning the induction of new vessel formation by FGF-2 in the ischemic heart have been promising (page 31, column 1, 2nd full paragraph). Watanabe et al. states that "Unger and associates delivered FGF-2 as an intracoronary bolus or intra-arterially and demonstrated enhanced angiogenesis and improvement of collateral blood flow in the dog subjected to progressive left circumflex coronary artery occlusion" (page 31, column 2, 2nd full paragraph).

Additionally, at the end of the previous Office Action, the Examiner cited Stegman et al. (Cardiac Vascul Regen 1: 259-267, 2000) and Freedman et al. (Ann Internal Med 136: 54-71, Jan 2002) as evidence of the state of the prior art. As pointed out by the Examiner, Stegman et al. teach the successful intramyocardial administration of FGF-1 to patients with chronic coronary artery disease (abstract). Freedman et al. disclose that angiogenic cytokines have been administered by diverse routes, including intracoronary and intramyocardial (page 58, column 1, last paragraph). Freedman et al. state that because local delivery of recombinant protein is probably ideal, clinical trials have favored intracoronary or intramyocardial routes (page 58, bottom of column 1 through the top of column 2; Tables 1 and 2). Thus, weighing all the teachings of the prior art, a person of ordinary skill is likely to understand that a disorder of a heart tissue involving loss or apoptosis of cardiomyocytes (such as acute myocardial ischemic

injury, as evidenced by Buja et al.), may be treatable by intramyocardial administration of a vascularization agent, such as FGF-2 or SDF-1.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of administering of SDF-1 to a subject suffering from ischemic cardiomyopathy, cerebrovascular ischemia, and myocardial ischemia as taught by Isner et al. by intramyocardially administering human SDF-1α or SDF-1β as taught by Rempel et al. and Watanabe et al. The person of ordinary skill in the art would have been motivated to make that modification in order to localize angiogenesis or induction of collateral vessels to the ischemic heart of the patient. The person of ordinary skill in the art reasonably would have expected success because (i) similar angiogenic growth factors were already being intramyocardially administered to the heart at the time the invention was made and (ii) SDF-1α and SDF-1β are isoforms encoded from the SDF-1 gene. Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

Since Isner et al. (in combination with Watanabe et al. and Rempel et al.) teach the administration of SDF-1 to the same subject population and to the same tissue as recited in the claims, the regeneration of endogenous cardiomyocytes must have been inherently occurring in the prior art. The disclosure of Isner et al. (in combination with Watanabe et al. and Rempel et al.) meets the terms of the claimed method because SDF-1 inherently possesses endogenous cardiomyocyte regeneration activity, absent evidence to the contrary (*In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977)). A compound and all of its properties are inseparable; they are one and the same thing and simply stating a new property of SDF-1 does not render the claimed method of the instant application free of the art (see *In re Papesch*, CCPA 137 USPQ

43; *In re Swinehart and Sfiligoj*, 169 USPQ 226 (CCPA 1971); *In re May*, 574 F.2d 1082, 1090, 197 USPQ 601, 607 (CCPA 1978)). Furthermore, inherent anticipation does not require that one of ordinary skill in the art recognize an inherent feature in a prior art disclosure (*Schering Corp. v. Geneva Pharmaceuticals Inc.*, 67 USPQ2d 1664 (CAFC 2003); *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004)).

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571)272-0881. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
11 May 2012

/Bridget E Bunner/
Primary Examiner, Art Unit 1647